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METHYLDOPA

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The blood pressure reducing effects of α-methyl-3,4-dihydroxy-dl-phenylalanine (methyldopa) were discovered by us in human hypertensive subjects in the fall of 1959 (Oates *et al.*, 1960). To that point in time, the compound had not been considered to have any intrinsic pharmacological activity and its therapeutic potential was not predictable. The compound was administered to patients because of its biochemical properties as a competitive inhibitor of dopa decarboxylase (1-aromatic amino acid-1-carboxylyase E.C.4.1.1.28), and as part of an ongoing clinical research programme on the interrelationships between alterations in vasoactive amine metabolism and blood pressure in patients with hypertension. Administration of doses sufficiently large (g quantities) to produce a biochemical (enzyme-inhibitory) effect in the intact human was an essential ingredient for discovery of the antihypertensive effects.

I believe that most discoveries are critically time-dependent and occur at a point when various elements in the research process can coalesce into a new development or concept. In the case of methyldopa, such a point in time was clearly October 16–18, 1958, when the first International Symposium on Catecholamines was held at the National Institute of Health in Bethesda, Maryland. My friend and colleague in the National Heart Institute, Dr Sidney Udenfriend, had organized this symposium at the request of the Pharmacology and Therapeutics Study Section of the N.I.H. and with the support of our Institute. Following the symposium, Sid and I discussed the various presentations in relationship to our own interests and decided that the dopa decarboxylase inhibitors, which had been discussed by both Clark (1959) and Holtz (1959), were ripe for further exploration in both laboratory animals and man. From a number of such compounds, we selected α-methyldopa and proceeded to contact friends in the pharmaceutical industry to obtain supplies of the compound. We soon learned that α-methyldopa had been synthesized and patented by Merck & Co., Inc. and accordingly on December 19, 1958, Sid called Dr Karl Pfister of Merck.

For a proper understanding of the events which were triggered by Udenfriend's call to Pfister, I feel it is essential to review our own research orientation as applied to hypertension, as well as Merck's side of the methyldopa story, during the several years *prior* to December, 1958. After having done this, I will recount details of the ensuing collaboration between Merck scientists and us, culminating in the development of methyldopa (Aldomet®). It seems unlikely, given the rigid regulatory requirements under which we operate presently, that a similar sequence of events could occur today.

Our side

An obvious question to be answered is: why were we interested and even enthusiastic in 1958 to study methyldopa in patients with hypertension. I believe one key to this was my own conviction by the mid-1950's that the screening of compounds for blood pressure effects in animal models (then extant) was a totally useless approach to the discovery of better antihypertensive drugs. I had come to believe that blood pressure data in animals were completely misleading, due to striking species differences in response, and the mode of administration used. Therefore, one needed another basis on which to decide to administer a compound in the only reliable test model, namely, the patient with hypertension. Two experiences had led me to this conclusion. The first arose from my participation, soon after joining the National Heart Institute in 1953 as a senior clinical investigator, in an internal screening programme of the Institute which was designed to discover new antihypertensive drugs. In this programme, natural products (generally alkaloid) were isolated from plants obtained through the U.S. Department of Agriculture by a group of chemists headed by Dr Evan C. Horning, and various 'extracts' were then supplied to Dr Neil C. Moran for pharmacological study. Compounds with 'worthwhile' blood pressure lowering properties in animals were then submitted to me for clinical testing, following completion of the appropriate toxicology. One compound, which produced marked vasodepressor responses in dogs, was an alkaloid derived from the seeds of *Ormosia panamensis* and was referred to as oxypanamine (cf. Moran *et al.*, 1959). Slowly and deliberately and

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under careful monitoring, we administered oxypanamine intravenously to hypertensive patients, gradually (over a period of weeks) increasing the dosage during individual infusions. We eventually reached a level of dosage which was known to be lethal in the dog, and yet were unable to lower the blood pressure of our patients. In fact, the only effect we could observe was residual discomfort (phlebitis) at the site of infusion. The second experience came later and related to our finding that several different monoamine oxidase inhibitors could be shown to have blood pressure lowering effects in human hypertensives, but not in experimental animals.

Thus, concurrently, I had become interested in developing indirect approaches which would by-pass animal pharmacology and specifically, had become fascinated by the possible importance of various 'pressor' amines produced endogenously. In those days, the best known ones were noradrenaline and adrenaline and a less obvious one was 5-hydroxytryptamine (5-HT). Possible relevance of the latter to the problem of hypertension was suggested to me by a report by Spies & Stone (1952) of striking pressor effects in human subjects of single intravenous injections of 0.5–5.0 mg of 5-HT. I believe it was in 1954 that someone who was aware of my interests suggested that I talk to a guy by the name of Udenfriend, a biochemist housed in another building on the N.I.H. 'reservation', who was said to be working on 5-HT. I learned shortly that Sid was a pioneer in the biochemistry of both the catecholamines and 5-HT and he soon convinced me that metabolic approaches might be more interesting than pharmacological ones. Accordingly, our first studies together focused on the role of monoamine oxidase (MAO) in the metabolism of 5-HT (Sjoerdsma *et al.*, 1955). Other biochemical technology developed by him was immediately applied to detailed investigations of biochemical abnormalities in patients with the malignant carcinoid syndrome as well as those with phaeochromocytoma. Along the way, and at the request of our research director, Dr Robert W. Berliner, I drew up a clinical research proposal for additional studies in hypertension. The essence of it consisted of determining the clinical and biochemical effects of inhibiting MAO in human hypertensives. It was already known that, paradoxically, 'hypotension', was a common side effect of treatment with 1-isonicotinyl-2-isopropyl hydrazide (iproniazid, Marsilid®). This proposal led us into extensive clinical investigations of the effects of several MAO inhibitors on aromatic amine metabolism and blood pressure (generally reduced).

Our groups became 'hot', so-to-speak, with many new 'recruits' interested in basic biochemistry joining Sid and young M.D.s interested in clinical investigation joining me (some worked for both of us). Members of my experimental therapeutics group in the late 1950's included Drs J. Richard Crout, Louis Gillespie, Jr., Leon I. Goldberg and John A. Oates. All of these men were later to contribute to the methyldopa story.

Chiefly, as a result of our studies with MAO inhibitors, we had come to the conclusion that decarboxylation to amines was a significant pathway of metabolism for all the aromatic amino acids. Further, we began to believe that biochemical manipulation of amine metabolism was a viable approach to discovery of new antihypertensive agents. If this did not prove to be the case, at least our results would constitute worthwhile clinical biochemical research. Other than metabolism by MAO, little was known about the fate of endogenous amines, except that storage in granules (e.g., noradrenaline in sympathetic nerves) represented an alternate fate and here too, manipulation by drugs (e.g. by rauwolfia alkaloids) resulted in control of high blood pressure.

Thus, it was a small step for us to become interested in a compound which might block aromatic amino acid decarboxylation. Besides, we had in hand all the techniques needed to study this reaction in the intact human. We also knew that an effective decarboxylase inhibitor should easily inhibit the formation of amines derived directly from dietary amino acids, but kinetic considerations made this result seem unlikely in the case of endogenous 5-hydroxytryptamine and noradrenaline, which are formed secondarily from 5-hydroxytryptophan and dopa, respectively. An exception might be (and proved to be) the case of tumours secreting these amines, e.g., carcinoid and phaeochromocytoma.

Merck's side

I judge that Karl Pfister, head of a small medicinal chemicals research group in the Merck organization during the 1950s (and now retired on a farm in Vermont), was the sustaining force behind the Merck programme on α-methylamino acids. The programme began in 1951 and was geared largely to the interests of outside experts. Thus in 1951, on the suggestion of Dr Eugene Roberts (then of Washington University, St Louis), a series of glutamic acid analogues were synthesized as possible anticancer drugs. The most striking result was that α-methylglutamic acid was found to be a potent inhibitor of glutamic acid decarboxylase. This resulted in a continued modest effort to synthesize other α-methylamino acids. During this same period, Dr Marcel Goldenberg of Columbia University had approached Merck with the suggestion that some dopa analogues be made which might inhibit catecholamine biosynthesis at the decarboxylase step and thereby perhaps prove useful in hypertension and other conditions. Various dopa analogues including α-methyl-

dopa were synthesized (Stein *et al.*, 1955) and supplied to Goldenberg for study of *in vivo* effects in animals, with a focus on catecholamine concentrations in adrenal glands. No pharmacological or biochemical activity was found, which is really not surprising in retrospect, since decarboxylation is not the rate-limiting step in catecholamine biosynthesis and turnover of these amines in adrenals is slow. During this same period (1951–1953), Dr Theodore L. Sourkes, then working at the Merck Institute, tested the compounds *in vitro* on dopa decarboxylase and found methyldopa to be among the most active inhibitors (Sourkes, 1954).

During 1953–58, the Merck effort was confined to supplying the compound as a biochemical tool to a small number of outside investigators, the most notable being those in Germany. In 1957, it was found by Dengler & Reichel (1958) of the University of Heidelberg that methyldopa administered intravenously prevented the blood pressure raising effects of exogenously administered dopa. At the same time, Westermann *et al.* (1958), working in Holtz's laboratory in Frankfurt, found that methyldopa also prevented pharmacological effects of 5-hydroxytryptophan (5-HTP) in guinea pigs and mice. These findings were among the first to indicate that dopa decarboxylase and 5-HTP decarboxylase were the same enzyme and were discussed at the catecholamine symposium in 1958.

In summary, by December, 1958, methyldopa had not been shown to have any direct pharmacological effects but sound evidence existed for its decarboxylase-inhibiting activity, both *in vitro* and *in vivo*. Some time after our discovery in man, I met Dr Westermann again and he indicated he had gone over various blood pressure records obtained in animals during his studies and still could not see a convincing direct effect of methyldopa.

The collaboration

In his call to Pfister, Udenfriend requested a supply of methyldopa for biochemical work in animals and suggested we have a meeting to discuss the possibility of studying the compound on the biochemistry of aromatic amino acids in humans. Pfister's reply was to the effect that they had no compound to send but that he would discuss the situation with his chief, Dr Max Tishler, President of Research for Merck. In late January, 1959, Drs Elmer Alpert (medical director), Richard W. Schayer and Karl Pfister visited us at the N.I.H. and apparently were impressed with our biochemical-clinical setup as well as our high level of interest. By February, 1959, Udenfriend had received a sample for biochemical studies and the decision had been taken at Merck to conduct subacute toxicity studies preparatory to clinical study. These were completed by the summer of 1959 and supplies for clinical use were made available by September. Despite the general lack of toxicity (e.g. LD-50s > 1.0 g/kg), the Merck suggestion was that maximal dosage be limited to about 300 mg. We suspected in advance that much more would be needed to produce a biochemical effect in man. Accordingly, Dr Louis Gillespie, Jr. (who had primary responsibility for care of our hypertensive patients) and Dr John A. Oates (who was to conduct the biochemical studies) began to work the dosage up in various patients and soon exceeded the 300 mg level. At the point when repeated single daily oral doses of 2.0 g were administered, a striking decrease in blood pressure was observed to occur. In passing, I should mention that the nature of our setup at the N.I.H. was such that patients could be kept in hospital for prolonged periods under close observation. Therefore, any drug effects would be apparent to us immediately even in a single patient. Additionally, relatively few patients studied under these conditions were sufficient to evaluate the effects of a drug. In other words, we didn't need statistics to prove that our results were significant.

Dramatic results in the one case were soon confirmed in a second and third and by mid-October, Max Tishler had directed that pilot plant production of the compound be started at Merck. By the first quarter of 1960, we had sufficient biochemical and clinical data in 10 hypertensive patients to submit our preliminary findings to *Science*, the paper being published in the June 24th issue (Oates *et al.*, 1960). In this paper, we reported on the inhibition of the decarboxylation of three exogenously-administered amino acids (5-hydroxytryptophan, tyrosine and tryptophan) to their corresponding amines, as indicated by levels of urinary excretion of the latter, as well as on the sedative and blood pressure reducing effects.

Despite our enthusiasm, it was still not certain that we had a new drug. My main concern was how frequently we would encounter the untoward reaction noted in our fourth case (and later shown to occur on rechallenge), consisting of fever, a grippe-like illness plus biochemical and clinical changes indicative of liver toxicity, albeit all rapidly reversible on withdrawal of drug. A second case of febrile reaction occurred during early trials with methyldopa but without evidence of liver injury (Gillespie *et al.*, 1962). Subsequently, we continued to see occasional reactions of this type and could show these were not due to impurities in the early batches of drug. Later such reactions were also observed during treatment with the l-isomer, or methyldopa (Horwitz & Sjoerdsma, 1963). Curiously, there followed a long lag period during which other clinicians failed to observe febrile and hepatic reactions. Eventually, of course, these and numerous other untoward effects came to be recognized (cf. McMahon, 1978).

There were some other hurdles on the way to methyldopa becoming a commercial drug. One of these was a considerable roadblock Udenfriend and I encountered in mid-1960, as I recall, during a visit to the Merck Institute. By this time, some 15–20 patients had been treated with methyldopa and we were becoming certain of our ground. Nonetheless, we were confronted with cross-currents of scepticism, particularly from the pharmacologists at Merck. This was because they had been unable to observe a blood pressure lowering effect of the drug in experimental animals, possibly due to the fact that anaesthetized preparations were generally used at that time. I had no problem with this situation for reasons stated earlier; in fact, that was the whole thrust of our research. Furthermore, there was understandable concern over the febrile-liver reactions we had observed, and considerable doubt existed that a satisfactory dosage form could be produced to enable daily drug dosing of 1.0–4.0 g, which were the amounts we were using. It seemed to us, at the time, that overall progress with the drug was painfully slow even after the dosage problem was resolved by demonstration (Gillespie *et al.*, 1962) that substantially all the biochemical and pharmacologic effects of the racemic drug (methyldopa) resided in the l-isomer (methyldopa, Aldomet®). During one of our last sessions with Merck, I distinctly recall being much relieved when Merck's international medical director, Dr K.C. Mezey, took me aside and said in essence, 'don't worry, Al, we believe you, and we'll have the drug on the market in England before it's sold in the U.S.' This proved to be so, the drug being marketed in England in April, 1962 and in the U.S. in May, 1963. In retrospect, of course, the period from discovery to commercial application seems remarkably fast in both instances.

It is my understanding that a final critical hurdle on the Merck side concerned 'cost of goods' since for every 2.0 g of d, l-α-methyldopa produced, only 1.0 g of the l-isomer could be recovered, ergo, an expensive process. I believe that this was eventually resolved at Merck in a process whereby the d-isomer could be recycled to make methyldopa.

Epilogue

Following our own flurry of publications (mostly uncited here) during the period 1960–1963, hundreds of additional papers have been published on methyldopa and the drug has now been in widespread clinical use for more than 15 years, alone or in combination with other drugs. Much has been written on the question of mechanism of action. There was a brief period when we came to question our own belief that methyldopa could not be acting by inhibition of endogenous catecholamine biosynthesis at the decarboxylase step. We soon came to recognize, however, that the hypotensive effects of methyldopa are mediated by amine metabolites of the compound which are formed via its own decarboxylation (Sjoedsma *et al.*, 1963). Also, I am sure that Lou Gillespie, John Oates and Dick Crout still recall how we wrote and argued and rewrote the discussion of an earlier paper (Gillespie *et al.*, 1962) and eventually came up with an intuitive statement to the effect that maybe the site of action of methyldopa or one of its metabolites lies within the central nervous system.

In closing, I wish to note that it has been a singular pleasure for me to tell the story of the discovery of methyldopa, and doubly so on the occasion of this 'festschrift' for Sir John McMichael. In savouring the sentiments of the moment, another more personal event comes to mind, which was also related specifically to my participation in this discovery. It occurred a few years ago when my son, Al Jr, then a university-level English major, was perusing a copy of The Book of Lists (Wallechinsky *et al.*, 1978) and with previously seldom-noted and unabashed respect in his eyes, looked up at me and said, 'hey Dad, did you know that Aldomet® is one of the 10 top-selling drugs in the country?'

I wish to thank Dr Sidney Udenfriend for helping me to recall many of the exciting events recited here. I am also grateful to Drs Roy Vagelos and Clement A. Stone of Merck, Sharp & Dohme Laboratories for providing me with copies of some of their internal documents on methyldopa, of which the most pertinent were memos written in 1959 and 1962 by Dr Karl Pfister.

Addendum: Dr Lou Gillespie died unexpectedly on September 20, 1981. I wish to dedicate this paper to his memory.

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